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ORIGINAL ARTICLE

Relationship between red cell distribution width and echocardiographic parameters in patients with diastolic heart failure

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Abstract Red cell distribution width (RDW) was found to be a prognostic marker in heart failure patients. The aim of the study was to investigate the relationship between RDW and echocardiographic parameters in diastolic heart failure (DHF). Seventy-one consecutive DHF patients (26 men) and 50 controls (21 men) were included in the study. All of the study population underwent echocardiographic evaluation, and blood samples were obtained. RDW and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values were significantly higher, whereas there was an increasing trend for high-sensitivity C-reactive protein levels in DHF patients than those in controls ($p < 0.001$, $p < 0.001$, and $p = 0.064$, respectively). All of the echocardiographic parameters evaluating diastolic function were more deteriorated in the DHF group. Patients who had an RDW value greater than the cutoff point also had higher NT-proBNP levels, an elevated ratio of mitral peak velocity of early diastolic filling to early diastolic mitral annular velocity, and increased estimated pulmonary capillary wedge pressures by tissue Doppler parameters, but lower creatinine clearance ($p < 0.05$ for all). According to the cutoff values calculated using receiver operating characteristic analysis, RDW > 13.6% and NT-proBNP > 125 pg/mL have high diagnostic accuracy for predicting DHF. RDW values were increased in the DHF population. Our results suggest that the high RDW levels in patients with DHF may be related to increased neurohormonal activity, impaired renal functions, and elevated filling pressure, but not to increased inflammation.

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Introduction

Diastolic heart failure (DHF) is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction, and abnormal diastolic function [1]. Various definitions, such as "heart failure with preserved systolic function" or "heart failure with normal or near normal ejection fraction" have also been used [2]. The proportion of patients with DHF in epidemiological studies ranges from 40% to 71% (mean, 56%), but in hospital-based cohort studies, it is slightly lower, ranging from 24% to 55% (mean, 41%) [3]. Older age; hypertension with left ventricular hypertrophy; pathologies, such as diabetes, obesity, coronary artery disease (CAD), and new onset atrial fibrillation are commonly associated with DHF [2,3].

Red cell distribution width (RDW) is a quantitative measure of anisocytosis, the variability in size of the circulating erythrocytes, and is routinely reported by automated laboratory equipment used to perform complete blood counts [4]. Higher RDW values indicate that a greater variety of cell sizes is present. In clinical practice, RDW is generally used to narrow the differential diagnosis of anemia, especially to differentiate iron deficiency anemia and thalassemia [5,6]. Recently, there has been growing attention given to the relationship between RDW and cardiovascular disorders, such as heart failure and CAD. This interest was spurred by the report from Felker et al. [7], which showed that there is a strong, independent association between RDW and the risk of adverse outcomes in heart failure patients, and the study by Tonelli et al. [8], which predicted a graded independent relationship between RDW and the risk of death and cardiovascular events in patients with CAD.

Although the prognostic importance of RDW in various cardiovascular diseases, including systolic heart failure, is well known, there are no data about RDW in the DHF population. The purpose of the present study was to determine if RDW levels are significantly different in DHF patients compared with those of controls and to investigate the relationship between RDW and echocardiographic parameters.

Design and methods

Study population

Seventy-one consecutive patients [mean age, 57 ± 7 years; 26 (37%) men] diagnosed with DHF in our clinic and 50 controls [mean age, 56 ± 7 years; 21 (42%) men] were included in the study. DHF was diagnosed when symptoms (dyspnea not associated with any other cause) and signs (rales or peripheral edema) of heart failure were observed along with a preserved left ventricular ejection fraction (LVEF $\geq$ 50%) and evidence of diastolic dysfunction. The control group was formed from voluntary individuals admitted to our clinic who did not have heart failure symptoms and signs and who had a preserved LVEF. Patients with systolic heart failure; hemodynamically unstable valvular heart disease; congenital heart disease; atrial fibrillation; chronic obstructive pulmonary disease; malignancy; known hematological diseases, such as hemolytic anemia, neoplastic metastases in the bone marrow; pregnancy; severe arthritis and inflammatory bowel diseases that can increase plasma RDW levels and other extracellular fluid increasing diseases, such as hypothyroidism and liver cirrhosis, were excluded from the study. The patient group was divided into two according to the most appropriate cutoff point of RDW calculated for predicting DHF (RDW $\leq$ 13.6%, RDW $>$ 13.6%).

The present study was a single-center study. All examinations were performed by the cardiology clinic of our hospital. All participants gave their informed consent before inclusion in the study. The study protocol was approved by the local committee at our institution.

Echocardiographic measurements

All of the study population underwent echocardiographic evaluation individually on the day of their admission (2.5-mHz transducer; Philips EnVisor C, Bothell, WA, USA). Standardized projections and measurements were performed for the evaluation of cardiac anatomy, ventricular function, and valve competence. LVEF was measured by Simpson's method [9]. Left ventricular mass was calculated by the formula described by Devereux et al., and left ventricular mass index was obtained by dividing the left ventricular mass by the body surface area [10]. The following conventional mitral inflow pulse wave Doppler parameters were measured: peak velocity of early diastolic filling and late filling, and deceleration time of the E-wave velocity. These parameters were obtained from the apical four-chamber view with a 1-mm to 3-mm sample volume placed between the mitral leaflet tips during diastole. Pulmonary venous flow parameters were also measured: peak systolic velocity (Ps), peak antegrade diastolic velocity (Pd), and the Ps/Pd ratio. These parameters were obtained from the apical four-chamber view with a 2-mm to 3-mm sample volume placed 1 cm into the pulmonary vein. Tissue Doppler parameters were measured: peak systolic mitral annular velocity, early diastolic mitral annular velocity (Em), and late diastolic mitral annular velocity (Am). These parameters were obtained from the apical four-chamber view with a 2-mm to 5-mm sample volume placed 1 cm within the septal and lateral insertions of the mitral leaflets. The mean of three or more measurements was used for analysis of the Doppler data. The ratio of mitral peak velocity of early diastolic filling to early diastolic mitral annular velocity (E/Em) was calculated for the lateral and septal annulus, and the mean of the lateral and septal E/Em were also determined. As previously described, the formula $(1.24 \times (E/\text{Em}) + 1.9)$ was used to estimate pulmonary capillary wedge pressure (PCWP) [11]. Diastolic dysfunction is defined as Em $<$ Am if Em is less than 10 cm/s in lateral mitral annulus or less than 8 cm/s in septal mitral annulus [12].

Biochemical measurements

Blood samples were obtained during admission for routine chemistry, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hs-CRP) after an overnight fast. RDW values were measured

with a Pentra DX 120 analyzer (ABX, Montpellier, France) in our hospital laboratory. NT-proBNP analyses were made by the electrochemiluminescence immunoassay method (Cobas 6000 analyzer; ROCHE Diagnostics GmbH, Mannheim, Germany), and hs-CRP analyses were made using the immunonephelometry method (Dade Behring, Inc., BN Prospect, Marburg, Germany) in our hospital laboratory. The Cockcroft-Gault formula was used to calculate creatinine clearance [13].

Statistical analysis

According to Kolmogorov-Smirnov normality test, two independent-sample *t* tests were used to compare the normally distributed independent variables between two groups, and Mann-Whitney *U* test was used to compare the non-normally distributed independent variables between two groups. Normally distributed continuous data were expressed as mean ± standard deviation; non-normally distributed continuous variables were presented as median and interquartile range (Quartiles l—3). Chi-square test was used for comparing the categorical data. Categorical data were expressed as count and percentages. A receiver operating characteristic (ROC) curve was constructed for RDW and NT-proBNP to test the effectiveness of various cutoff points in predicting DHF. The area under the ROC curve was calculated; the sensitivity and specificity for the RDW and NT-proBNP of the most appropriate cutoff point were calculated for predicting DHF. Spearman's correlation test was used for correlation between variables. A multivariate logistic regression model was implemented to determine RDW, NT-proBNP, and other covariates associated with DHF. A p value less than 0.05 was considered statistically significant. Statistical analysis was performed by using commercial software (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY, USA).

Results

Baseline characteristics and the differences between the patient and the control groups

There were no significant differences between the patient and the control groups with regard to age, sex, hypertension, diabetes, CAD, smoking, medications, body mass index, fasting blood glucose, thyroid status, lipid profile, creatinine clearance, serum creatinine, and hemoglobin levels (Table 1). The patient group had higher blood pressure, more hypertrophy in the left ventricle, and a bigger left atrial size (Tables 1 and 2). RDW and NT-proBNP were significantly higher in the patient group [RDW: 12.99% ± 1.34% *vs.* 14.33% ± 1.53%, $p < 0.001$; NT-proBNP: 57 pg/L (26—94 pg/L) *vs.* 97 pg/L (57—264 pg/L), $p < 0.001$] (Table 1). hs-CRP was also higher in the patient group, but this difference did not reach significant levels [3.19 mg/dL

Table 1 Baseline characteristics and laboratory findings of patient and control groups.

Variables	Control ($n = 50$)	Patient ($n = 71$)	p
Age (y)	56.16 ± 6.98	57.09 ± 7.43	0.491
Gender (male)	21 (42.0)	26 (36.6)	0.550
Hypertension	24 (48.0)	43 (60.6)	0.171
Diabetes	14 (28.0)	20 (28.2)	0.984
Coronary artery disease	10 (20.0)	21 (29.6)	0.235
Smoking	10 (20.0)	13 (18.3)	0.816
Renin-angiotensin system blockers	15 (30.0)	33 (46.5)	0.068
β-Blockers	12 (24.0)	23 (32.4)	0.316
Calcium channel blockers	9 (18.0)	10 (14.1)	0.560
Statins	8 (16.0)	14 (19.7)	0.602
Aspirin	19 (38.0)	26 (36.6)	0.877
Body mass index (kg/m^2)	30.30 ± 4.10	31.33 ± 4.14	0.179
Systolic blood pressure (mmHg)	130.00 ± 20.73	139.79 ± 20.06	0.011
Diastolic blood pressure (mmHg)	81.00 ± 11.65	86.41 ± 11.75	0.014
Glucose (mg/dL)	100 (92—115)	105 (92—122)	0.218[a]
Thyroid stimulating hormone (μIU/mL)	1.54 ± 0.95	1.44 ± 0.95	0.597
Creatinine (mg/dL)	0.76 ± 0.18	0.78 ± 0.23	0.469
Creatinine clearance (mL/min/1.73 m^2)	115.79 ± 28.17	113.01 ± 33.76	0.638
Cholesterol (mg/dL)	198.31 ± 39.94	196.24 ± 42.20	0.788
Triglyceride (mg/dL)	164.37 ± 86.34	152.61 ± 62.35	0.388
Low-density-lipoprotein cholesterol (mg/dL)	125.43 ± 32.79	125.37 ± 36.71	0.992
High-density-lipoprotein cholesterol (mg/dL)	44.00 ± 11.17	46.85 ± 11.93	0.190
Hemoglobin (g/dL)	13.75 ± 1.64	13.38 ± 1.53	0.208
Red cell distribution width (%)	12.99 ± 1.34	14.33 ± 1.53	<0.001
N-terminal pro-B-type natriuretic peptide (pg/mL)	57 (26—94)	97 (57—264)	<0.001[a]
High-sensitivity C-reactive protein (mg/L)	3.19 (3.19—5.60)	3.27 (3.22—4.46)	0.064

Data are shown as *n* (%), mean ± standard deviation, or median (interquartile range).
[a] Calculated by log-transformed data.

Table 2 Echocardiographic parameters of patient and control groups.

Variables	Control ($n = 50$)	Patient ($n = 71$)	p
Left ventricular ejection fraction (%)	68 (63–73)	72 (63–75)	0.339
Left ventricular end-diastolic dimension (mm)	47.06 ± 5.84	46.27 ± 5.42	0.445
Left ventricular end-systolic dimension (mm)	29.66 ± 4.68	30.21 ± 4.52	0.516
Interventricular septal dimension (mm)	10.70 ± 1.94	11.69 ± 1.95	0.007
Posterior wall dimension (mm)	9 (9–11)	11 (10–12)	<0.001
Left atrium diameter (mm)	34.18 ± 4.14	38.04 ± 5.48	<0.001
Left ventricular mass index (g/m^2)	91.02 ± 20.38	103.11 ± 24.33	0.005
Ratio of peak systolic velocity and peak antegrade diastolic velocity of pulmonary venous flow	1.3 (1.1–1.4)	0.9 (0.8–1.3)	0.001
E (cm/s)	65.14 ± 17.45	77.87 ± 20.30	<0.001
A (cm/s)	78.18 ± 22.41	83.81 ± 22.98	0.182
E/*A*	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.157
Deceleration time of the E-wave velocity (ms)	211.38 ± 46.27	215.99 ± 43.48	0.577
Lateral			
Sm (cm/s)	9.37 ± 2.03	8.91 ± 2.11	0.232
Em (cm/s)	10.87 ± 1.81	8.70 ± 1.91	<0.001
Am (cm/s)	11.64 ± 2.38	11.88 ± 2.88	0.619
Em/Am	0.87 (0.75–1.20)	0.72 (0.64–0.85)	<0.001
E/Em	6.06 ± 1.56	9.43 ± 3.33	<0.001
PCWP (mmHg)	9.00 (7.98–10.82)	12.63 (11.36–15.44)	<0.001
Septal			
Sm (cm/s)	8.11 ± 1.45	7.65 ± 1.61	0.112
Em (cm/s)	8.72 ± 1.25	6.70 ± 1.56	<0.001
Am (cm/s)	10.54 ± 1.76	10.31 ± 2.26	0.548
Em/Am	0.85 ± 0.18	0.66 ± 0.14	<0.001
E/Em	7.53 ± 2.02	12.11 ± 3.89	<0.001
PCWP (mmHg)	11.24 ± 2.50	16.92 ± 4.82	<0.001
E/Em mean	6.46 (5.33–7.96)	9.85 (8.74–11.45)	<0.001
PCWP mean (mmHg)	9.91 (8.51–11.77)	14.12 (12.74–16.09)	<0.001

Data are shown as mean ± standard deviation or median (interquartile range).
A = peak velocity of late filling; Am = late diastolic mitral annular velocity; *E* = peak velocity of early diastolic filling; *E*/Em = early mitral inflow velocity to early diastolic mitral annular velocity ratio; Em = early diastolic mitral annular velocity; PCWP = pulmonary capillary wedge pressure; Sm = peak systolic mitral annular velocity.

(3.19–5.60 mg/dL) *vs.* 3.27 mg/dL (3.22–4.46 mg/dL), $p = 0.064$] (Table 1). The mitral *E*; lateral, septal, and mean *E*/Em; and the PCWP estimated from each of the *E*/Em measurements were all significantly higher, whereas Ps/Pd, lateral and septal Em, and lateral and septal Em/Am were significantly lower in the patient group (Table 2).

Relationship between RDW and study parameters

The most appropriate cutoff point calculated for predicting DHF was 13.6%. The patients who had an RDW value equal or less than 13.6% were included in the "lower RDW" group. The remaining formed the "higher RDW" group.

There were no significant differences between the lower and higher RDW groups with regard to age, sex, diabetes, CAD, smoking, medications except statin and aspirin, body mass index, fasting blood glucose, thyroid status, and hemoglobin levels (Table 3). Hypertension was significantly higher in the "higher RDW" group, but systolic and diastolic blood pressures were similar (Table 3). Cholesterol levels were lower, and the number of patients on statin therapy was higher in the "higher RDW" group (Table 3). Serum creatinine was significantly higher, and creatinine clearance was significantly lower in the "higher RDW" group (Table 3). There were no significant differences in the LVEF, left ventricular mass index, Ps/Pd ratio, *E*/*A*, and lateral and septal Em/Am of the "lower RDW" and "higher RDW" groups (Table 4). The mean *E*/Em and estimated mean PCWP were significantly higher in the "higher RDW" group (Table 4). NT-proBNP was significantly higher in the "higher RDW" group, but this difference was not seen in the hs-CRP levels (Table 4).

RDW positively correlated with NT-proBNP ($p < 0.001$, $r = 0.373$); mean *E*/Em ($p < 0.001$, $r = 0.385$); estimated mean PCWP ($p < 0.001$, $r = 0.385$); and hs-CRP ($p = 0.007$, $r = 0.246$) in the study population. When we performed the same analysis for DHF patients, results were significant for NT-proBNP ($p = 0.004$, $r = 0.316$); mean *E*/Em ($p = 0.035$, $r = 0.227$); and estimated mean PCWP ($p = 0.035$, $r = 0.227$), but not for hs-CRP ($p = 0.093$, $r = 0.202$).

According to the cutoff values calculated using ROC analysis, RDW > 13.6% and NT-proBNP > 125 pg/mL have high diagnostic accuracy for predicting DHF (area under the ROC curve = 0.736, $p < 0.001$ and area under the ROC curve = 0.725, $p < 0.001$, respectively). There was also no significant difference for diagnostic accuracy between the

Table 3 Baseline characteristics and laboratory findings of lower and higher RDW groups.

Variables	Lower RDW (≤13.6%) ($n = 25$)	Higher RDW (>13.6%) ($n = 46$)	p
Age (y)	57 ± 7	57 ± 8	0.924
Gender (male)	8 (32)	18 (39)	0.551
Hypertension	10 (40)	33 (71)	0.009
Diabetes	8 (24)	14 (30)	0.565
Coronary artery disease	7 (28)	14 (30)	0.830
Smoking	3 (12)	10 (22)	0.311
Renin-angiotensin system blockers	8 (32)	25 (54)	0.071
β-Blockers	6 (24)	17 (37)	0.265
Calcium channel blockers	3 (12)	7 (15)	0.710
Statins	0 (0)	14 (30)	0.002
Acetyl salicylic acid	4 (16)	22 (48)	0.008
Body mass index (kg/m^2)	32 ± 4	31 ± 4	0.707
Systolic blood pressure (mmHg)	137 ± 20	141 ± 20	0.463
Diastolic blood pressure (mmHg)	87 ± 11	86 ± 12	0.838
Glucose (mg/dL)	111 ± 33	118 ± 40	0.494
Thyroid stimulating hormone (μIU/mL)	1.19 ± 0.78	1.58 ± 1.01	0.102
Creatinine (mg/dL)	0.58 ± 0.78	0.90 ± 0.21	<0.001
Creatinine clearance (mL/min/1.73 m^2)	140 ± 26	97 ± 27	<0.001
Cholesterol (mg/dL)	214 ± 50	187 ± 34	0.008
Triglyceride (mg/dL)	152 ± 55	153 ± 67	0.927
Low-density-lipoprotein cholesterol (mg/dL)	139 ± 43	118 ± 30	0.016
High-density-lipoprotein cholesterol (mg/dL)	48 ± 12	46 ± 12	0.434
Hemoglobin (g/dL)	13.9 ± 1.2	13.1 ± 1.6	0.057
N-terminal pro-B-type natriuretic peptide (pg/mL)	70 (57–106)	191 (57–560)	0.006[a]
High-sensitivity C-reactive protein (mg/L)	4.33 ± 2.22	5.05 ± 3.74	0.227

Data are shown as n (%), mean ± standard deviation, or median (interquartile range).
RDW = red cell distribution width.
[a] Calculated by log-transformed data.

two methods ($p = 0.898$) (Table 5 and Fig. 1). According to multivariate logistic regression model (adjusted for systolic and diastolic blood pressure and left atrium diameter), when RDW value increases by 1 unit, risk of DHF increases 1.84 times, and when NT-proBNP value increases by 1 unit, risk of DHF increases 1.01 times (Table 6).

Discussion

This study has shown that the RDW is elevated in the DHF population, and that higher RDW levels are associated with higher NT-proBNP levels and elevated left ventricular filling pressures (LVFPs) in DHF patients.

Table 4 Echocardiographic parameters of lower and higher RDW groups.

Variables	Lower RDW (≤13.6%) ($n = 25$)	Higher RDW (>13.6%) ($n = 46$)	p
Left ventricular ejection fraction (%)	70 ± 8	68 ± 7	0.279
Left ventricular mass index (g/m^2)	104 ± 26	103 ± 24	0.865
Ratio of peak systolic velocity and peak antegrade diastolic velocity of pulmonary venous flow	0.9 (0.8–1.3)	0.9 (0.8–1.2)	0.887
Ratio of peak velocity of early diastolic filling to peak velocity of late filling	0.81 (0.69–0.97)	0.87 (0.74–1.06)	0.133
Ratio of early mitral inflow velocity to early diastolic mitral annular velocity, lateral	0.72 ± 0.14	0.79 ± 0.25	0.198
Ratio of early diastolic mitral annular velocity to late diastolic mitral annular velocity, septal	0.63 ± 0.11	0.68 ± 0.15	0.229
Ratio of early mitral inflow velocity to early diastolic mitral annular velocity, mean	9.4 (8.7–10.1)	10.6 (8.5–14.0)	0.047
Pulmonary capillary wedge pressure, mean (mmHg)	13 (13–14)	15 (12–19)	0.047

Data are shown as mean ± standard deviation or median (interquartile range).
RDW = red cell distribution width.

Table 5 Comparison of diagnostic accuracy for diastolic heart failure between RDW and NT-proBNP.

Variables	Cutoff value	AUC	95% CI of AUC	Sensitivity	Specificity	p^a	p^b
RDW (%)	>13.6	0.736	0.648—0.812	0.648	0.700	<0.001	0.898
NT-proBNP (pg/mL)	>125.0	0.725	0.635—0.803	0.449	0.960	<0.001	—

AUC = area under the receiver operating characteristic curve; CI = confidence interval; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RDW = red cell distribution width.
[a] Significant level of AUC.
[b] Comparison between RDW and NT-proBNP.

RDW is a quantitative measure of anisocytosis, which is the variability in size of the circulating erythrocytes, and is routinely measured by automated laboratory equipment used to perform complete blood counts [4]. There are several hematological reasons for elevated RDW, such as iron deficiency anemia, hemolytic disorders, vitamin B_{12} and folate deficiency, and thrombotic thrombocytopenic purpura [14—17]. It has also been shown that RDW levels are elevated in stroke, colon cancer, inflammatory bowel disease, pregnancy, and pulmonary hypertension [18—22]. Moreover, RDW has been found to be the predictor of all-cause deaths in two community-based cohorts [23,24]. Recently, RDW has been shown to be a novel marker for predicting outcomes in the heart failure population [7,25,26]. It has been concluded that RDW independently predicts 1-year mortality after an acute heart failure episode, and high RDW values also predict poor long-term outcome regardless of anemia status in acute heart failure patients [27,28]. High RDW values are also associated with increased risk of death and cardiovascular events in people with prior myocardial infarction without symptomatic heart failure, all-cause mortality in an unselected population referred for coronary angiography, mortality after acute myocardial infarction, adverse outcomes in patients with acute coronary syndrome, and long-term mortality in patients undergoing percutaneus coronary intervention [8,29—32].

There are several potential mechanisms to explain elevated RDW values in heart failure. Previous studies have addressed inflammation, ineffective erythropoiesis, malnutrition, impaired renal function, and neurohormonal activation in heart failure patients [26].

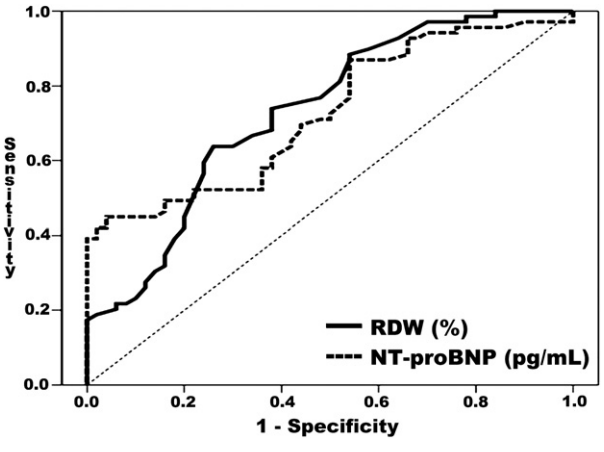

Figure 1. Receiver operating characteristic curve showing the relationship between sensitivity and false positivity at various cutoff points for red cell distribution width (RDW) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) to predict diastolic heart failure.

Because our study is the first to evaluate the relationship between RDW and DHF, there is no information about the possible mechanism for RDW elevation in this population. According to Kitzman et al. [33], neurohormonal abnormalities similar to those observed in systolic heart failure occur in DHF. In the present study, RDW was shown to be correlated both with NT-proBNP and hs-CRP for our study population, but the correlation between hs-CRP and RDW remained insignificant for the patient group. Moreover, there were also no significant differences in hs-CRP values between the patient and the control groups. This suggests that neurohormonal activation may be more effective for RDW elevation in this population than inflammation. Van Kimmenade et al. [27] also demonstrated that the elevation of RDW in acute heart failure patients did not appear to be associated with nutritional status, transfusion history, or inflammation. On the other hand, Allen et al. [34] very recently showed that elevated RDW may indicate inflammatory stress and impaired iron mobilization in heart failure population.

Previous studies show that elevated NT-proBNP values are diagnostic of DHF and are associated with elevated LVFP [35,36]. It has been found that there is a strong correlation between NT-proBNP and E/Em, and a threshold of 269.1 pg/mL of NT-proBNP predicted an $E/Em > 15$ with 90% sensitivity and 73% specificity in DHF [37]. The positive correlation between elevated RDW and NT-proBNP, E/Em, and PCWP in our study implies that increases in LVFP could be the underlying mechanism for RDW elevation in patients with DHF. Oh et al. [38] found that there is an association between RDW elevation and E/Em in acute heart failure patients, and that the optimal cutoff value of RDW for predicting $E/Em > 15$ is 13.45%. We observed significant differences related to NT-proBNP, mean E/Em, and estimated mean PCWP values in the two groups divided according to the cutoff value of RDW for predicting DHF (13.6%). Hampole et al. [22] found that in patients with pulmonary hypertension and right heart failure, elevated RDW is associated with mortality, but there is no correlation with hemodynamic parameters. Based on this finding, the elevation in RDW is not only explained by hemodynamic abnormalities.

Renal functions were significantly more impaired in our "higher RDW" group. Förhécz et al. [26] previously addressed impaired renal function as one of the possible mechanism for RDW elevation in patients with heart failure. A similar mechanism may also be responsible for the higher RDW values in DHF patients.

Table 6 Comparison of diastolic heart failure and RDW and NT-proBNP in multivariate logistic regression model.

Variables	β	OR	95% CI for OR	*p*
RDW	0.609	1.838	1.284–2.630	0.001
Systolic blood pressure	0.022	1.022	1.001–1.044	0.042
Left atrium diameter (mm)	0.156	1.169	1.057–1.293	0.002
NT-proBNP	0.011	1.011	1.003–1.019	0.006
Systolic blood pressure	0.046	1.047	1.008–1.088	0.017
Left atrium diameter (mm)	0.141	1.151	1.037–1.278	0.008

CI = confidence interval; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio; RDW = red cell distribution width.

The lower cholesterol levels in our "higher RDW" group can be explained by the greater proportion of patients on statin therapy. Our DHF group had higher systolic blood pressure, more hypertrophy in the left ventricle, and bigger left atrial size. This is an expected result because hypertension-hypertrophy is one of the etiologies of DHF.

There are potential limitations of this study. First, the sample size was relatively small. Second, despite the evidences that *E*/Em is a good noninvasive predictor of LVFP, we did not measure left ventricular pressures directly. Third, we did not measure vitamin B_{12} and folate levels, which are one of the potential causes of increased levels of RDW. However, our study population is not anemic, and the possible effect of these vitamin deficiencies may be unimportant. Fourth, we also did not evaluate the nutritional status, which has been previously suggested as a potential cause of RDW increase. Finally, it may not be true to suggest that neurohormonal activation is the major underlying mechanism for RDW elevation in DHF population according to the correlation found between RDW and NT-proBNP alone. Measurements of renin, angiotensin II, and epinephrine can help make more accurate inferences.

In conclusion, RDW values were increased in the DHF population. Our results suggest that high RDW levels in patients with DHF may be related to increased neurohormonal activity, impaired renal functions, and elevated filling pressure, but not to increased inflammation. RDW can be used as an additive marker for predicting elevated LVFP in patients with DHF at no additional cost. However, further studies are required to solve the underlying mechanism for the RDW increase in this population.

References

[1] Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002;105: 1387–93.

[2] Chatterjee K, Massie B. Systolic and diastolic heart failure: differences and similarities. J Card Fail 2007;13:569–76.

[3] Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. J Am Coll Cardiol 2004;43:317–27.

[4] Morris M, Davey FR. Basic examination of blood. In: Henry JB, editor. Clinical diagnosis and management by laboratory methods. 20th Ed. Philadelphia, PA: W.B. Saunders Company; 2001. p. 489–99.

[5] McKenzie SD. Introduction to anemia. In: McKenzie SD, editor. Clinical laboratory hematology. Saddle River, NJ: Pearson Prentice-Hall; 2003. p. 161–88.

[6] Demir A, Yarali N, Fisgin T, Duru F, Kara A. Most reliable indices in differentiation between thalassemia trait and iron deficiency anemia. Pediatr Int 2002;44:612–6.

[7] Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007;50: 40–7.

[8] Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation 2008;117:163–8.

[9] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008;10:933–89.

[10] Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.

[11] Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.

[12] Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.

[13] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

[14] Gupta AD, Hegde C, Mistri R. Red cell distribution width as a measure of severity of iron deficiency in iron deficiency anaemia. Indian J Med Res 1994;100:177–83.

[15] Docci D, Delvecchio C, Gollini C, Turci F, Baldrati L, Gilli P. Red blood cell volume distribution width (RDW) in uraemic patients on chronic haemodialysis. Int J Artif Organs 1989;12: 170–4.

[16] Nagajothi N, Braverman A. Elevated red cell distribution width in the diagnosis of thrombotic thrombocytopenic purpura in patients presenting with anemia and thrombocytopenia. South Med J 2007;100:257–9.

[17] Bessman D. What's an RDW? Am J Clin Pathol 1981;76:242–3.

[18] Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci 2009;277:103–8.

[19] Spell DW, Jones Jr DV, Harper WF, Bessman JD. The value of a complete blood count in predicting cancer of the colon. Cancer Detect Prev 2004;28:37—42.
[20] Clarke K, Sagunarthy R, Kansal S. RDW as an additional marker in inflammatory bowel disease/undifferentiated colitis. Dig Dis Sci 2008;53:251—3.
[21] Shehata HA, Ali MM, Evans-Jones JC, Upton GJ, Manyonda IT. Red cell distribution width (RDW) changes in pregnancy. Int J Gynaecol Obstet 1998;62:43—6.
[22] Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol 2009;104:868—72.
[23] Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. Arch Intern Med 2009;169:515—23.
[24] Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med 2009;169:588—94.
[25] Al-Najjar Y, Goode KM, Zhang J, Cleland JG, Clark AL. Red cell distribution width: an inexpensive and powerful prognostic marker in heart failure. Eur J Heart Fail 2009;11:1155—62.
[26] Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009;158:659—66.
[27] van Kimmenade RR, Mohammed AA, Uthamalingam S, van der Meer P, Felker GM, Januzzi Jr JL. Red blood cell distribution width and 1-year mortality in acute heart failure. Eur J Heart Fail 2010;12:129—36.
[28] Pascual-Figal DA, Bonaque JC, Redondo B, Caro C, Manzano-Fernandez S, Sánchez-Mas J, et al. Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. Eur J Heart Fail 2009;11:840—6.
[29] Cavusoglu E, Chopra V, Gupta A, Battala VR, Poludasu S, Eng C, et al. Relation between red blood cell distribution width (RDW) and all-cause mortality at two years in an unselected population referred for coronary angiography. Int J Cardiol 2010;141:141—6.
[30] Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol 2010;105:312—7.
[31] Nabais S, Losa N, Gaspar A, Rocha S, Costa J, Azevedo P, et al. Association between red blood cell distribution width and outcomes at six months in patients with acute coronary syndromes. Rev Port Cardiol 2009;28:905—24.
[32] Poludasu S, Marmur JD, Weedon J, Khan W, Cavusoglu E. Red cell distribution width (RDW) as a predictor of long-term mortality in patients undergoing percutaneous coronary intervention. Thromb Haemost 2009;102:581—7.
[33] Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144—50.
[34] Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail 2010;16:230—8.
[35] Dahlström U. Can natriuretic peptides be used for the diagnosis of diastolic heart failure? Eur J Heart Fail 2004;6:281—7.
[36] Nakao S, Goda A, Yuba M, Otsuka M, Matsumoto M, Yoshida C, et al. Characterization of left ventricular filling abnormalities and its relation to elevated plasma brain natriuretic peptide level in acute to chronic diastolic heart failure. Circ J 2007;71:1412—7.
[37] Tuğcu A, Yildirimtürk O, Aytekin S. The diagnostic value of N-terminal B-type natriuretic peptide in diastolic heart failure: comparison with echocardiographic findings. Turk Kardiyol Dern Ars 2009;37:112—21.
[38] Oh J, Kang SM, Hong N, Choi JW, Lee SH, Park S, et al. Relation between red cell distribution width with echocardiographic parameters in patients with acute heart failure. J Card Fail 2009;15:517—22.